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| 10/720,904 | 11/24/2003 | George Sgouros | D6348CIP | 5297 |
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| PERREIRA, MELISSA JEAN | | | | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/720,904

Applicant(s)

SGOUROS ET AL.

Examiner

MELISSA PERREIRA

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-59 is/are pending in the application.
- 4a) Of the above claim(s) 1-19 and 34-59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20-33 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-8508)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/26/09 has been entered.

Priority

2. Claims 20-33 are granted benefit of the priority date 12/16/02 of the parent document 10/319,978. Support for the recitation, "entrapping said radionuclide within small liposomal vesicles; incorporating said entrapped radionuclide into the aqueous phase of large liposomes" of the instant claims 20-33 was not found in the provisional 60/212,186.

Previous Claims and Rejections Status

3. Claims 1-59 are pending in the application. Claims 1-19 and 34-59 are withdrawn from consideration as being drawn to nonelected groups I, III and IV.

4. The rejection of claims 20-33 under 35 U.S.C. 103(a) as being unpatentable over Larsen et al. (US 6,592,843) in view of Scheinberg et al. (6,683,162B2) and Wartchow et al. (US2003/0082103A1) is withdrawn.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 24 and 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear as to what "engineered molecules or fragments thereof" would include. It is unclear what compounds would be encompassed by the terms "engineered molecules or fragments thereof" thus the metes and bounds are not defined as the specification fails to define such "engineered molecules or fragments thereof". Further, such "engineered molecules or fragments thereof" are not recognized terms of the art.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 20-33 are provisionally rejected on the ground of nonstatutory

obviousness-type double patenting as being unpatentable over claims 1-5, 7-8, 10-17, 29-55 of copending Application No. 10/319978. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed a method of targeting cells in an individual for liposomal delivery of an alpha particle-emitting radionuclide thereto with reduced systemic release of radioactive decay intermediates comprising the steps of: entrapping passively said radionuclide within small liposomal vesicles; incorporating said entrapped radionuclide into the aqueous phase of large liposomes, said liposomes having a diameter sufficient to retain at least a majority of the radioactive decay intermediates of said radionuclide. It would have been obvious to one of ordinary skill in the art at the time of the present invention to modify the claims of the copending application in order to produce a method.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

10. Claims 20-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larsen et al. (US 6,592,843) in view of Wartchow et al. (US2003/0082103A1) and in further view of Pikul et al. (*Arch. Surg.* **1987**, 122, 1417-1420) and Presant et al. (US 5,441,745).

11. Larsen et al. (US 6,592,843) discloses the method of targeting cells in an individual/human via the administration of radionuclide-liposome conjugates to treat malignancies, such as cancer, leukemia, etc. (column 6, lines 35-38 and 55-59). The preparation of the radionuclide-liposome conjugator systems involve encapsulation of radionuclides that emit alpha particles, such as ^{212}Pb , ^{225}Ac into a liposome containing PEG affinic groups and an agent which is capable of maintaining the desired pH in the internal aqueous medium (column 2, lines 37-62; column 3, lines 3-13 and 34-46). The resulting radionuclide-liposome conjugator system is stabilized in a PBS solution (phosphate containing buffer) (example 2). The radionuclide is chelated to EDTA, DTPA, etc. to form a chelation compound and is actively incorporated into the liposomal vesicle with the help of an ionophore (column 3, lines 43-46), thus yielding liposomes that are of the typical size of 100nm (column 3, line 13). The trapping of ^{212}Pb in a high concentration of chelator within the liposome avoids the release of the daughter product where the conjugator system traps the daughter nuclide, ^{212}Bi , within the liposome after nuclear transformation (column 5, lines 7-24). The PEG grafted liposomes allow for the conjugation of targeting ligands, such as folate conjugated monoclonal antibodies

(column 2, lines 37-62; column 5, lines 58-65; column 6, lines 1-18) to target the radionuclide-liposome conjugator systems to desired cells. Increased levels of tumor uptake due to sustained blood concentrations are thereby achieved (column 1, lines 45-50). Larsen et al. does not disclose the incorporation of the radionuclide containing small liposome into a large liposome having a diameter of about 600 to about 1000 nm or labeling the small vesicle with biotin or herceptin.

12. Wartchow et al. (US2003/0082103A1) discloses radiotherapeutic liposomal constructs comprising a radionuclide-chelator (DOTA) conjugation compound, targeting entity (antibody) and stabilizing entity (PEG) (p1, [0002]; p7, [0054]; p8, [0055-0057]; p10, [0077] and [0084]). The radiotherapeutic liposomal constructs are used for the method of targeting cancerous tissue with radionuclides upon administration to a subject while leaving healthy tissue unaffected (p1, [0003]; p13, [0101]). The liposomes of the disclosure may be bilayer structures that may have the therapeutic agent (i.e. radionuclide) passively encapsulated as a radionuclide-chelator (p9, [0075]), the membrane bilayers typically encapsulate an aqueous volume containing active drugs and the resulting MUV are of the size 1000 nm (p10, [0078-0079]). These multilamellar vesicles (MUV) are rapidly taken up into the reticuloendothelial system (the liver and spleen) which causes them to remain in the circulatory system for hours (p10, [0079]). The targeting agents may include herceptin, biotin, etc. (p11, [0089]; p12, [0099]; p14, [0105]).

13. Larsen et al. also does not disclose the passive incorporation of the radionuclide into a liposome,

14. Pikul et al. (*Arch. Surg.* **1987**, 122, 1417-1420) discloses the preparation of liposomes containing dextran- $^{212}\text{Pb}/^{212}\text{Bi}$ via passively capturing/encapsulating the solution of dextran- $^{212}\text{Pb}/^{212}\text{Bi}$ in the aqueous center of a large, unilamellar liposome (as evidenced by Larsen et al. (US 6,592,843) column 14, lines 28-29; column 1, lines 59-64). The diameter of the resulting liposome is from 350-500 nm (p1417, paragraph 3 and carrier vehicle: liposomes). ^{212}Pb is a more attractive radiation source than ^{212}Bi as it has a half-life of 10.6 hours and decays to its α -emitting daughter ^{212}Bi (abstract; p1417, paragraph 2).

15. At the time of the invention it would have been obvious to one ordinarily skilled in the art that dextran- $^{212}\text{Pb}/^{212}\text{Bi}$ may be passively encapsulated into the liposomes of Larsen et al. as Pikul et al. teaches of the passive encapsulation of dextran- $^{212}\text{Pb}/^{212}\text{Bi}$ into liposomes and Larsen et al. states that dextran- $^{212}\text{Pb}/^{212}\text{Bi}$ is passively incorporated into the aqueous phase (i.e. the interior of the liposome) (Larsen et al. column 1, lines 59-64).

16. At the time of the invention it would have been obvious to one ordinarily skilled in the art that the liposomal radionuclide-conjugator complex of Larsen et al. may be multilamellar (MUV) and thus contain a radiolabeled small liposome within a large liposome as Warthchow et al. teaches that radiotherapeutic liposomal constructs may be encapsulated within the MUV (i.e. multilamellar vesicle radionuclide-conjugator complexes). The MUV's of Warthchow et al. provides for the limitation of a radiolabeled

small liposome contained within a large liposome as the multilamellar vesicles have an onion like form (Wartchow et al. p10, [0078]). The references of Larsen et al. and Wartchow et al. are drawn to the same utility, such as radionuclide-chelator liposomal conjugator systems and therefore one skilled in the art would have a reasonable expectation of success for preparing such a multilamellar liposome.

17. Wartchow et al. teaches of PEG containing liposomal vesicles for the attachment of targeting groups while Larsen et al. also teaches of PEG containing liposomal vesicles and therefore one would have a reasonable expectation of success for attaching any targeting agent, such as herceptin or biotin to the liposomes of Larsen et al. for site specificity, such as targeting cancerous tissue with radionuclides upon administration of the liposomal vesicles while leaving healthy tissue unaffected (Wartchow et al. p1, [0003]; p13, [0101]).

18. In regards to the instant claim 22, Larsen et al. does not disclose the preinjection of an empty liposome saturating the reticuloendothelial organs.

19. Presant et al. (US 5,441,745) discloses the enhancement of the movement of the phospholipid vesicles to the tumors in a patient's body by introducing an empty phospholipids vesicle into the patient's blood stream to block uptake by the reticuloendothelial cells of the liver, spleen and other tissues in the patient's body prior to the administration of the phospholipid vesicle containing a labeling agent (i.e. radioisotope) (column 3, lines 65+; column 4, lines 1-26; fig 3; column 8, lines 33-55).

20. At the time of the invention it would have been obvious to one skilled in the art to provide for a reticuloendothelial blockade, which involves the prior administration of empty liposomes, to ensure for the enhanced uptake of the labeled phospholipid vesicle to tumors and reduced uptake by healthy tissues of the liver, spleen, etc. for the method of targeting cells in an individual/human of Larsen et al.

Response to Arguments

21. Applicant's arguments filed 3/26/09 have been fully considered but they are not persuasive.

22. Applicant asserts that Larsen et al. discloses the preparation of the liposomes using an active incorporation of radionuclides via ionophores.

23. The reference of Larsen et al. was not used to teach of the passive incorporation of radionuclides into liposomes but was used to teach of the encapsulation of radionuclides that emit alpha particles, such as ^{212}Pb , ^{225}Ac into a liposome to generate a radionuclide-liposome conjugator system containing PEG affinic groups. The radionuclide-liposome conjugator system avoids the release of the daughter product and the conjugator system traps the daughter nuclide, ^{212}Bi , within the liposome after nuclear transformation (Larsen et al. column 5, lines 7-24). Pikul et al. was used to teach of the passive encapsulation of dextran- $^{212}\text{Pb}/^{212}\text{Bi}$ into liposomes. Therefore it would have been obvious to one skilled in the art that the encapsulation of dextran- $^{212}\text{Pb}/^{212}\text{Bi}$ into the liposomes of Larsen et al., which traps the daughter nuclide (^{212}Bi), does not require an ionophore.

24. Applicant asserts that Wartchow et al. does not disclose larger liposomes having a diameter of about 600-1000nm.
25. Wartchow et al. teaches of liposomes (MUV) are of the size 1000 nm (Wartchow et al. p10, [0078-0079]) which encompasses the limitations of about 600 nm to about 1000 nm of the instant claims.
26. Applicant asserts that no combination of the references suggest the attachment of antibodies directly onto the PEG-lipid surface.
27. Wartchow et al. teaches of PEG containing liposomal vesicles for the attachment of targeting groups while Larsen et al. also teaches of PEG containing liposomal vesicles and therefore one would have a reasonable expectation of success for attaching any targeting agent, such as herceptin or biotin to the liposomes of Larsen et al. for site specificity, such as targeting cancerous tissue with radionuclides upon administration of the liposomal vesicles while leaving healthy tissue unaffected (Wartchow et al. p1, [0003]; p13, [0101]).

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618